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L1: Entry 5 of 6 File: USPT Mar 17, 1998

US-PAT-NO: 5728379
DOCUMENT-IDENTIFIER: US 5728379 A

TITLE: Tumor- or cell-specific herpes simplex virus replication

DATE-ISSUED: March 17, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Martuza; Robert L.	Chevy Chase	MD		
Rabkin; Samuel D.	Bethesda	MD		
Miyatake; Shin-ichi	Ohtsu			JP

US-CL-CURRENT: 424/93.2; 435/320.1, 435/456

CLAIMS:

What is claimed is:

1. A replication-competent herpes simplex virus comprising a tumor-specific tissue-specific or cell-specific transcriptional regulatory sequence that is operatively linked to an essential herpes simplex virus gene, transcriptional regulatory sequence that is operatively linked to an essential herpes simplex virus gene, wherein said transcriptional regulatory sequence effects expression of said gene in a specific tumor, tissue or cell, such that said virus replicates only in said tumor, tissue or cell.

2. A herpes simplex virus vector, wherein the genome of said viral vector contains a tumor-specific or tissue-specific or cell-specific transcriptional regulatory sequence that is operatively linked to an essential herpes simplex virus gene, wherein said transcriptional regulatory sequence effects expression of said gene in a specific tumor, tissue or cell, such that said virus replicates only in said tumor, tissue or cell.

3. A method for killing tumor cells in a subject, comprising the step of administering to said tumor cells a pharmaceutical composition that is comprised of

(A) a herpes simplex virus that contains a tumor-specific promoter that is operatively linked to an essential herpes simplex virus gene; and

(B) a pharmaceutically acceptable vehicle for said virus, such that said tumor cells are infected in situ by said virus, whereby said tumor cells are killed.

4. The method of claim 3, wherein said tumor cells are of a type selected from the group consisting of melanoma cells, pancreatic cancer cells, prostate carcinoma cells, breast cancer cells, lung cancer cells, colon cancer cells, lymphoma cells, hepatoma cells, mesothelioma and epidermoid carcinoma cells.

5. A method fo preparing a tumor-specific or tissue-specific or cell-specific replication-competent herpes simplex virus, said method comprising the step of:

permanently altering the genome of a herpes simplex virus so that the virus (1) kills tumor cells and (2) lacks general virulence against normal cells and (3) contains a tumor-specific or tissue-specific or cell-specific transcriptional regulatory sequence that is operatively linked to an essential herpes simplex virus gene.

6. The method of claim 5, wherein said herpes simplex virus is HSV-1.

7. The method of claim 5, wherein said herpes simplex virus is HSV-2.

8. A method for ablating specific normal cells in a subject, comprising the step of administering to said cells a pharmaceutical composition composed of

(A) a herpes simplex virus that contains a tissue-specific or cell-specific transcriptional regulatory sequence that is operatively linked to an essential herpes simplex virus gene, wherein said transcriptional regulatory sequence effects expression of said gene in a specific tissue or cell, such that said virus replicates only in said tissue or cell; and

(B) a pharmaceutically acceptable vehicle for said virus, such that said specific normal cells are infected in situ by said virus, whereby said cells are killed.

9. The method of claim 8, wherein said normal cells are pituitary cells and said cell-specific transcriptional regulatory sequence is the growth hormone promoter.

10. The method of claim 8, wherein said normal cells are adrenocortical cells and said cell-specific transcriptional regulatory sequence is the Pro-opiomelanocortin promoter.

11. A method for killing tumor cells in a subject, comprising the steps of administering to said tumor cells a herpes simplex virus, wherein said virus comprises a tumor cell-specific transcriptional regulatory sequence wherein said transcriptional regulatory sequence controls expression of at least one viral protein necessary for viral replication and wherein said transcriptional regulatory sequence in said virus is induced selectively so that said virus replicates in the tumor cells at a level that is at least about two log orders higher than in normal cells, whereby said tumor cells are killed.

12. The replication-competent herpes simplex virus of claim 1, wherein said essential herpes simplex virus gene is an HSV immediate-early gene.

13. The replication-competent herpes simplex virus of claim 12, wherein said HSV immediate-early gene is the ICP4 gene.

WEST Search History

DATE: Friday, December 13, 2002

Set Name side by side	Query	Hit Count	Set Name result set
DB=DWPI; PLUR=YES; OP=ADJ			
L2	Pyles R B.in.	1	L2
DB=USPT; PLUR=YES; OP=ADJ			
L1	Martuza Robert	6	L1

END OF SEARCH HISTORY

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L15: Entry 1 of 3 File: DWPI Oct 24, 2002

DERWENT-ACC-NO: 2002-537524
DERWENT-WEEK: 200273

TITLE: Expressing heterologous nucleic acid sequence in a vascular cell for treating cardiovascular diseases, involves administering to the cell a genetically engineered herpes simplex viral vector comprising the sequence

INVENTOR: ROIZMAN, B; SCHWARTZ, L B ; WEICHSELBAUM, R R

PRIORITY-DATA: 2000US-253680P (November 28, 2000), 2001US-0995475 (November 28, 2001)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 20020155432 A1	October 24, 2002		000	C12Q001/70
WO 200245431 A2	June 6, 2002	E	114	C12N000/00
AU 200217885 A	June 11, 2002		000	H04N007/173

INT-CL (IPC): A61 K 39/12; A61 K 39/245; A61 K 39/255; A61 K 39/265; A61 K 39/27; C12 N 0/00; C12 N 15/00; C12 N 15/09; C12 N 15/63; C12 N 15/70; C12 N 15/74; C12 P 21/06; C12 Q 1/70; H04 N 7/173

ABSTRACTED-PUB-NO: WO 200245431A
BASIC-ABSTRACT:

NOVELTY - Expressing (M) a heterologous nucleic acid sequence in a vascular cell, or inducing normal physiology in a functionally abnormal vascular cell, comprising administering to the cell a recombinant replicating herpes simplex viral (HSV) vector having a heterologous nucleic acid, where HSV is debilitated for growth in the central nervous system.

ACTIVITY - Cardiant; Antiarrhythmic; Vasotropic.

To demonstrate in vivo gene transfer in proliferating vascular tissue, the external jugular vein of male New Zealand white rabbits was exposed to vehicle, HSVlacZ (R849), or adeno-associated virus (AAV)lacZ. Male New Zealand white rabbits were anesthetized, the external jugular vein was exposed and two branches cannulated with 24-gauge catheters. One cannula was used for irrigation and infection, and the other for intralumenal pressure monitoring. The main channel was infected with either vehicle, AAVlacZ 4 multiply 1011 plaque forming units (pfu)/ml, or HSVlacZ (R849) 4 multiply 108 pfu/ml for 10 minutes at 100 mmHg. Following infection, the vein was irrigated with saline, excised and bivalved. The ipsilateral common carotid artery (CCA) was exposed through the same incision and the animal systemically anticoagulated with heparin (200 U/kg) intravenously. The CCA was doubly clamped and a 1.5-cm longitudinal arteriotomy made proximal to the cranial thyroid branch. The arteriotomy was reconstructed with external jugular vein patch angioplasty using running 8-0 polypropylene suture. Ultrasonic transit-time flow through the graft was measured. There was no significant difference in mean blood flow in vehicle-treated vs. Viral-infected patches at time of implantation. The incision was closed and the animal was allowed to recover. After four weeks, the vein patches were harvested and assessed for patency and beta -galactosidase expression using X gal. Intraarterial pressure and blood flow through the patch were again measured and recorded. All vein patches that had been exposed to HSVlacZ showed significant beta -galactosidase expression in all layers of the vein wall at 4 weeks after exposure, especially within the smooth muscle cells comprising the neointima (48

plus or minus 2 % infection efficiency). In contrast, patches infected with AAVlacZ showed inconsistent transgene expression, mostly confined to the adventitia. Expression was not evident in the vehicle-exposed patches or in any harvested external jugular veins or CCAs contralateral to an HSVlacZ (R849)-infected vein patch or an AAV-infected vein patch.

MECHANISM OF ACTION - Gene therapy.

USE - (M) is useful for expressing a heterologous nucleic acid sequence encoding a polypeptide such as antiproliferative polypeptide, vasodilatory polypeptide, and an angiogenic polypeptide, an antisense oligonucleotide or antisense polynucleotide complementary to the polypeptide in a vascular cell, such as endothelial cell, smooth muscle cell or adventitial cell. (M) is also useful for inducing normal physiology in a functionally abnormal vascular cell. (M) is useful for treating or preventing a cardiovascular disease or condition such as chronic heart failure, hypertensive cardiovascular disease, ischemic heart disease, arrhythmia, congenital heart disease, valvular heart disease or stenotic defect, cardiomyopathy, aneurysm, chronic venous insufficiency, peripheral arterial disease or restenosis, in a vascular cell. The heterologous nucleic acid sequence is expressed in vascular tissue for a duration of more than 7, 14, 21, 28, 35 or 70 days. The heterologous nucleic acid sequence encodes a screenable or selectable marker, an antithrombotic nucleic acid, angiogenesis regulating nucleic acid, immunomodulator, inducer of cellular proliferation, inhibitor of cellular proliferation or a regulator or programmed cell death. The method further comprises administering at least one pharmacological agent such as antihyperlipoproteinemic agent, antiarteriosclerotic agent, antithrombotic/fibrinolytic agent, blood coagulant, antiarrhythmic agent, antihypertensive agent, vasopressor, treatment agent for congestive heart failure, antianginal agent, anti-infection agent, to the vascular cell. (All claimed).

ADVANTAGE - (M) provides therapeutic benefit both in vascular and cardiovascular tissue.

ABSTRACTED-PUB-NO: WO 200245431A
EQUIVALENT-ABSTRACTS:

CHOSEN-DRAWING: Dwg.0/0

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(71) Applicant: THE UNIVERSITY OF CHICAGO [US/US]; Office of Intellectual Property and Technology Transfer, 5640 South ellis Street, Suite 405, Chicago, IL 60637 (US).

(72) Inventors: SCHWARTZ, Lewis, B.; 510 N. Clay Street, Hinsdale, IL 60521-3214 (US). WEICHSELBAUM, Ralph, R.; 1909 N Burlington Street, Chicago, IL 60614-5123 (US). ROIZMAN, Bernard; 5555 S. Liverett Street, Chicago, IL 60637-1968 (US).

(74) Agent: CAWLEY, Thomas, A., Jr.; Marshall, Gerstein & Borun, 6300 Sears Tower, 233 S. Wacker Drive, Chicago, IL 60606 (US).

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WO 02/45431 A2

(54) Title: GENETICALLY ENGINEERED HERPES VIRUS FOR THE TREATMENT OF CARDIOVASCULAR DISEASE

(57) Abstract: The present invention provides methods of expressing a nucleic acid or producing a proteinaceous composition encoded by a nucleic acid in vascular and cardiovascular cells by administration of a herpesvirus vector. The present invention provides methods of producing a therapeutic benefit in vascular and cardiovascular tissue by administration of a herpesvirus vector. In additional aspects, the invention concerns combination therapies for vascular and cardiovascular diseases comprising administration of a herpesvirus vector and treatment with at least addition pharmacological agent or surgical procedure.